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(54) **Title:** ANTI-INFECTIVE ACTIVE SUBSTANCE COMBINATIONS AND THE USE THEREOF FOR THE TOPICAL TREATMENT OF FUNGUS DISEASES OF TOE AND FINGER NAILS

(54) **Bezeichnung:** ANTIINFEKTIVE WIRKSTOFFKOMBINATIONEN UND IHRE VERWENDUNG ZUR TOPISCHEN BEHANDLUNG VON PILZERKRANKUNGEN DER FUSS- UND FINGERNÄGEL

(57) **Abstract:** The invention relates to a preparation containing an active substance combination comprised of a topical antimycotic agent, of a systemic antimycotic agent, and of a physiologically safe lacquer base. The inventive preparation is suited for treating onychomycoses. The invention preferably uses water-insoluble lacquer preparations and a combination of at least one systemic antimycotic agent from the group containing itraconazole, terbinafine, fluconazole or the salts thereof with at least one topical antimycotic agent from the group containing ciclopirox 6-(2,4,4-trimethylpentyl)-1-hydroxy-4-methyl-2 (1H)-pyridone, amorolfine and butenafine or the salts thereof.

(57) **Zusammenfassung:** Eine Zubereitung, enthaltend eine Wirkstoffkombination aus einem topischen und einem systemischen Antimykotikum und einer physiologisch unbedenklichen Lackgrundlage eignet sich zur Behandlung von Onychomykosen. Bevorzugt werden wasserunlösliche Lackzubereitungen und eine Kombination von mindestens einem systemischen Antimykotikum aus der Gruppe Itraconazol, Terbinafin und Fluconazol oder deren Salze mit mindestens einem topischen Antimykotikum aus der Gruppe Ciclopirox, 6-(2,4,4-trimethylpentyl)-1-hydroxy-4-methyl-2 (1H)-pyridon, Amorolfin und Butenafin oder deren Salze eingesetzt.

WO 01/66145 A1

Description

Antiinfective active ingredient combinations and their use for the topical treatment of fungal infections of the toenails and fingernails

Fungal infections of the toenails and fingernails (onychomycoses) are widespread around the world. This chronic pathological entity, which does not tend to heal by itself, is becoming increasingly important particularly in highly developed industrialized countries. Onychomycoses constitute the commonest disorder of nails, comprising a proportion of up to 40%. The prevalence of onychomycoses is stated in the state of the art to be 2.8% to 8.4%. Mycoses of nails now account for about 30% of all dermatomycoses. Epidemiological studies show that 20% to 30% of patients with Tinea pedis also have onychomycosis.

Many patients feel restricted in their social contacts especially when the onychomycosis is located on the fingernails where it is clearly visible. In addition, the pathological event results in a possible restriction of tactility, motility and manual abilities. The need for treatment also derives from the fact that onychomycoses contribute, as source of infection, to the spread of the disease from the nail to the free skin. In addition, they represent a risk of infection for a continually increasing population.

Since the early 1990s a large number of new treatment methods for the therapy of onychomycosis has been developed. These are, on the one hand, novel systemically active antimycotics; for example itraconazole, see US 4,267,179; (E)-N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalene-methanamine, which is also called terbinafine, and α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)-1H-1,2,4-triazol-1-ethanol, which is also called fluconazole, but also lacquer preparations to be used topically, which make the treatment of onychomycoses more promising.

Experience has shown that systemic therapy may occasionally lead to serious, unwanted side effects of pharmaceuticals which may, in some circumstances, be life-threatening, because the active ingredient must reach the site of infection via the blood circulation. Side effects and interactions with other medicines are unavoidable in particular in many elderly patients with multimorbidity. Systemic antimycotics additionally have

other unwanted concomitant effects such as gaps in the range of pathogens which can be treated or, in some cases, unreliable absorption.

Various studies have very recently been carried out with antimycotic-containing lacquer preparations in combination with systemic itraconazole or terbinafine therapy on patients with pronounced onychomycosis. The results show that the combination of a topical lacquer preparation with a systemic administration of itraconazole or terbinafine is distinctly superior to monotherapy with itraconazole and terbinafine for the therapy of severe onychomycoses. Results to date indicate that the rate of unsuccessful systemic therapy of onychomycoses can be considerably reduced by combination therapy with a topically active antimycotic-containing lacquer preparation and a systemically active antimycotic.

A disadvantage of combined treatment with a topical and a systemic antimycotic in the therapy of onychomycoses is still the stress on the system with all the adverse effects connected therewith for the patient even with this treatment strategy. Another important disadvantage here is the small amount of systemic antimycotic which reaches the toenail or fingernail. In addition, it has to date been possible only with very complicated and drastic methods to apply systemic antimycotics such as itraconazole in therapeutically effective concentrations topically to the toenail or fingernail (see WO 96/19186).

It is an object of the present invention to provide a formulation which does not have the known disadvantages associated with the described topical/systemic combination therapy of onychomycoses.

Contrary to the existing technical prejudice, that systemic antimycotics such as itraconazole penetrate into the nail in sufficient concentration on topical application only after breaking the sulfur bridges in the nail keratin and through addition of urea (WO 96/19186), it has now been found, surprisingly, that combinations of topical with systemic antimycotics in a lacquer base are able after topical application, without the abovementioned measure and the addition mentioned, to penetrate in and through the nail in therapeutically effective concentrations. In addition, patients treated with a systemic antimycotic show only comparatively low concentrations of the antimycotic in the toenail or fingernail.

The invention therefore relates to pharmaceutical preparations comprising a combination of a topical and a systemic antimycotic active ingredient in a physiologically acceptable lacquer base.

The invention relates in particular to a pharmaceutical preparation comprising a water-insoluble film former, at least one systemic antimycotic from the group of itraconazole, terbinafine and fluconazole and/or physiologically tolerated salts of itraconazole, terbinafine and fluconazole, and at least one topical antimycotic from the group of ciclopirox, 6-(2,4,4-trimethylpentyl)-1-hydroxy-4-methyl-2(1H)-pyridone, amorolfine and butenafine and/or physiologically tolerated salts of ciclopirox, 6-(2,4,4-trimethylpentyl)-1-hydroxy-4-methyl-2(1H)-pyridone, amorolfine and butenafine, or a mixture of more than one of the abovementioned antimycotics or salts thereof.

Preferred pharmaceutical preparations comprise ciclopirox (which is also called 6-cyclohexyl-1-hydroxy-4-methyl-2(1H)-pyridone) and itraconazole, or butenafine hydrochloride and fluconazole, or ciclopirox and fluconazole, or amorolfine hydrochloride and terbinafine hydrochloride, as antimycotic.

The abovementioned topical or systemic antimycotics are employed both in free form and as physiologically tolerated salts. If organic bases are used for the salts, the bases preferably employed are of low volatility, for example low molecular weight alkanolamines such as ethanolamine, diethanolamine, N-ethylethanolamine, N-methyldiethanolamine, triethanolamine, diethylaminoethanol, 2-amino-2-methyl-n-propanol, dimethylaminopropanol, 2-amino-2-methylpropanediol, triisopropanolamine. Further bases of low volatility which may be mentioned are, for example, ethylenediamine, hexamethylenediamine, morpholine, piperidine, piperazine, cyclohexylamine, tributylamine, dodecylamine, N,N-dimethyldodecylamine, stearylamine, oleylamine, benzylamine, dibenzylamine, N-ethylbenzylamine, dimethylstearylamine, N-methylmorpholine, N-methylpiperazine, 4-methylcyclohexylamine, N-hydroxyethylmorpholine. The salts of quaternary ammonium hydroxides such as trimethylbenzylammonium hydroxide, tetramethylammonium hydroxide or tetraethylammonium hydroxide can also be used, as can guanidine and its derivatives, in particular its alkylation products. However, it is also possible to employ as salt formers, for example, low molecular weight alkylamines such as methylamine, ethylamine or triethylamine. Salts with inorganic cations, for example alkali

metal salts, in particular sodium, potassium or ammonium salts, in particular hydrochlorides, alkaline earth metal salts such as, in particular, the magnesium or calcium salt, and salts with doubly charged to quadrupally charged cations, for example the zinc, aluminum or zirconium salt, are also suitable for the compounds to be employed according to the invention.

The invention further relates to the use of a combination of a topical and a systemic antimycotic active ingredient in a physiologically acceptable lacquer base for producing a topical pharmaceutical preparation for the prophylactic and therapeutic treatment of fungal infections of the toenails and fingernails.

The invention also relates to the use of a water-insoluble film former, at least one systemic antimycotic from the group of itraconazole, terbinafine and fluconazole and/or physiologically tolerated salts of itraconazole, terbinafine and fluconazole, and at least one topical antimycotic from the group of ciclopirox, 6-(2,4,4-trimethylpentyl)-1-hydroxy-4-methyl-2(1H)-pyridone, amorolfine and butenafine and/or physiologically tolerated salts of ciclopirox, 6-(2,4,4-trimethylpentyl)-1-hydroxy-4-methyl-2(1H)-pyridone, amorolfine and butenafine, or a mixture of more than one of the above-mentioned antimycotics or salts thereof, for producing a topical pharmaceutical preparation for the prophylactic and therapeutic treatment of fungal infections of the toenails and fingernails.

The content of topical and systemic active ingredient in the lacquer preparations according to the invention depends on the structure of each active ingredient and thus on its release from the lacquer film, its penetration characteristics in the nail and its antifungal properties.

The topical active ingredient is generally present in an amount of from 0.25 to 20 percent by weight, preferably 2 to 15 percent by weight, in the pharmaceutical preparations according to the invention for the therapy of onychomycoses, which are employed as nail lacquer, i.e. the solvent-containing use form. The content of "systemic" active ingredient is generally from 0.05 to 10 percent by weight, preferably 0.1 to 5 percent by weight.

The nail lacquers according to the invention comprise apart from the active ingredient dissolved in a solvent or solvent mixture as necessary

ingredients also one or more film formers which, after drying of the preparation, form a water-insoluble film on the nail.

Examples of substances suitable as film formers are based on cellulose nitrate or physiologically acceptable polymers like those customary, for example, in cosmetics, preferably mixed with cellulose nitrate. Mention may be made, for example, of polyvinyl acetate and partially hydrolyzed polyvinyl acetate, copolymers of vinyl acetate on the one hand and acrylic acid or crotonic acid or monoalkyl maleate on the other hand, ternary copolymers of vinyl acetate on the one hand and crotonic acid and vinyl neodecanoate or crotonic acid and vinyl propionate on the other hand, copolymers of methyl vinyl ether and monoalkyl maleate, in particular as monobutyl maleate, copolymers of fatty acid vinyl ester and acrylic acid or methacrylic acid, copolymers of N-vinylpyrrolidone, methacrylic acid and alkyl methacrylate, copolymers of acrylic acid and methacrylic acid or alkyl acrylate or alkyl methacrylate, polyvinyl acetates and polyvinylbutyrals, alkyl-substituted poly-N-vinylpyrrolidones, alkyl esters from copolymers of olefins and maleic anhydride and products of the reaction of rosin with acrylic acid. The alkyl radicals in the esters are usually short-chain and mostly have not more than four carbon atoms.

The preparations preferably employed comprise a water-insoluble film former from the group of copolymer of ethyl acrylate/methyl methacrylate/ trimethylammonioethyl methacrylate chloride, copolymer of acrylic and methacrylic ester with proportions of trimethylammoniumethyl methacrylate chloride, copolymer of methyl vinyl ether and monobutyl maleate, polymer of polyvinylbutyral and cellulose nitrate or copolymer of methacrylic acid and ethyl acrylate.

Suitable physiologically acceptable solvents are substances like the hydrocarbons, halogenated hydrocarbons, alcohols, ethers, ketones and esters customary in cosmetics, in particular acetic esters of monohydric alcohols such as ethyl and butyl acetates, where appropriate mixed with aromatic hydrocarbons such as toluene and/or alcohols such as ethanol or isopropanol.

The combination of the solvents is well known to be crucially important for the drying time, spreadability and other important properties of the lacquer or lacquer film. The solvent system preferably consists of an optimal

mixture of low boilers (= solvents with a boiling point of up to 100°C) and medium boilers (= solvents with a boiling point of up to 150°C), where appropriate with a small proportion of high boilers (= solvents with a boiling point of up to 200°C).

The nail lacquers according to the invention may additionally comprise additives customary in cosmetics, such as phthalate- or camphor-based plasticizers, dyes and colored pigments, pearlescent agents, sedimentation inhibitors, sulfonamide resins, silicates, fragrances, wetting agents such as sodium dioctyl sulfosuccinate, lanolin derivatives, photoprotective agents such as 2-hydroxy-4-methoxybenzophenone, substances with antibacterial activity, and substances with keratolytic and/or keratoplastic effect, such as urea, allantoin, enzymes and salicylic acid.

Colored or pigmented nail lacquers have the advantage, for example that the preparation according to the invention can be suited to the patient's esthetic perception, and the existing changes in the nails are not directly visible to other people.

A process for producing the water-insoluble nail lacquers consists of mixing the physiologically acceptable lacquer base in dissolved form with the antimycotics, and further processing the preparation where necessary.

The antimycotics are generally present in the pharmaceutical preparations according to the invention in an amount of from 2 to 80 percent by weight, preferably from 10 to 60 percent by weight, and in particular from 20 to 40 percent by weight, in each case based on the amount of the involatile ingredients, which is the total of the film formers, of the pigments, plasticizers and other involatile additives present where appropriate, and of the effective antimycotics employed.

It is possible with the lacquer preparations according to the invention to achieve a thorough cure on treatment of onychomycoses - without the occurrence of systemic side effects and drug interactions. In the light of experience with therapy to date, this is an exceptionally important finding. A further advantage is the considerably shorter treatment time with the pharmaceutical preparation according to the invention. This is shown in particular in the considerably higher concentrations of the systemic antimycotics in the nail after topical application.

The pharmaceutical preparations according to the invention are also suitable for prophylactic use against onychomycoses, in which case a sufficiently large deposit of active ingredient is achieved in the nail so that, in the event of fungal contamination, there is no outbreak of a nail infection caused by fungi. The pharmaceutical preparations used for prophylaxis comprise small amounts of the antimycotics employed for therapy. The active ingredient is preferably generally employed in an amount of from 0.25 to 4 percent by weight, preferably 1 to 4 percent by weight, in the pharmaceutical preparations for prophylaxis of onychomycoses, which are employed as nail lacquer, i.e. the solvent-containing use form. The content of "systemic" active ingredient is generally from 0.05 to 3 percent by weight, preferably 0.1 to 1 percent by weight. Compared with systemic monotherapy, a considerably smaller amount of substance is necessary for building up an appropriate depot of active ingredient.

The invention also relates to the use of the preparations according to the invention in cosmetics.

The present invention is explained in detail by the following examples, but is not confined to these. Unless otherwise noted, the stated amounts are based on weight.

Example 1	
Amorolfine hydrochloride	5.0%
Terbinafine hydrochloride	2.5%
Copolymer of acrylic and methacrylic ester with proportions of trimethylammoniumethyl methacrylate chloride (e.g. EUDRAGIT RL 100)	20.0%
Isopropyl myristate	2.5%
Isopropyl alcohol	70.0%

Example 2	
Butenafine hydrochloride	5.0%
Fluconazole	5.0%
Copolymer of methyl vinyl ether and monobutyl maleate	25.0%
96% ethanol	65.0%

Example 3	
Ciclopirox	8.0%
Itraconazole	0.5%
Isopropyl myristate	5.0%
1,2-propylene glycol	4.0%
Copolymer of methyl vinyl ether and monobutyl maleate	7.5%
Ethyl acetate	25.0%
Isopropyl alcohol	50.0%

Example 4	
Ciclopirox	7.5%
Fluconazole	5.0%
Copolymer of methyl vinyl ether and monobutyl maleate	15.0%
Ethyl acetate	30.0%
96% ethanol	42.5%

Example 5

The active ingredient combination after application of the preparations according to the invention was determined in the nail by HPLC measurements after extraction of distal nail material obtained on cutting the nails of volunteers.

After treatment 2 × a week for 6 weeks, the values found for the preparation of Example 3 were as follows:

itraconazole	800 ng/g of nail
ciclopirox	140 µg/g of nail

After oral administration of 100 mg of itraconazole each day for 3 months, the itraconazole concentration revealed in the prior art in the distal nail plate is 100 ng/g of nail. It is therefore possible by the pharmaceutical preparation according to the invention to achieve in a short time itraconazole concentrations in the nail which are about eight times higher than through systemic treatment.

Example 6

After treatment 2 × a week for 2 weeks, the values found for the preparation of Example 4 were as follows:

fluconazole	17 µg/g of nail

ciclopirox	92 µg/g of nail

Patent claims:

1. A preparation comprising a water-insoluble film former, and a combination of active ingredients comprising at least one antimycotic from the group of itraconazole, terbinafine and fluconazole and/or physiologically tolerated salts of itraconazole, terbinafine and fluconazole, and
at least one antimycotic from the group of ciclopirox, 6-(2,4,4-trimethylpentyl)-1-hydroxy-4-methyl-2(1H)-pyridone, amorolfine and butenafine and/or physiologically tolerated salts of ciclopirox, 6-(2,4,4-trimethylpentyl)-1-hydroxy-4-methyl-2(1H)-pyridone, amorolfine and butenafine, or a mixture of more than one of the abovementioned antimycotics or salts thereof.

2. The preparation as claimed in claim 1, comprising as antimycotics
ciclopirox and itraconazole, or
butenafine hydrochloride and fluconazole, or
ciclopirox and fluconazole, or
amorolfine hydrochloride and terbinafine hydrochloride.

3. The preparation as claimed in claim 1 or 2, comprising as physiologically acceptable lacquer base a film former based on cellulose nitrate, polyvinyl acetate and partially hydrolyzed polyvinyl acetate, copolymers of vinyl acetate on the one hand and acrylic acid or crotonic acid or monoalkyl maleate on the other hand, ternary copolymers of vinyl acetate on the one hand and crotonic acid and vinyl neodecanoate, or crotonic acid and vinyl propionate on the other hand, copolymers of methyl vinyl ether and monoalkyl maleate, in particular as monobutyl maleate, copolymers of fatty acid vinyl ester and acrylic acid or methacrylic acid, copolymers of N-vinylpyrrolidone, methacrylic acid and alkyl methacrylate, copolymers of acrylic acid and methacrylic acid or alkyl acrylate or alkyl methacrylate, polyvinyl acetates and polyvinyl butyrals, alkyl-substituted poly-N-vinylpyrrolidones, alkyl esters from copolymers of olefins and maleic anhydride and products of the reaction of rosin with acrylic acid; the alkyl radicals in the esters are usually short-chain and have not more than four carbon atoms.

4. The preparation as claimed in claim 3, comprising as water-insoluble film former a copolymer of ethyl acrylate/methyl methacrylate/trimethylammonioethyl methacrylate chloride, copolymer of acrylic and methacrylic ester with proportions of trimethylammoniumethyl methacrylate chloride, copolymer of methyl vinyl ether and monobutyl maleate, polymer of polyvinylbutyral and cellulose nitrate or a copolymer of methacrylic acid and ethyl acrylate.

5. The preparation as claimed in one or more of claims 1 to 4, comprising an antimycotic from the group of ciclopirox, 6-(2,4,4-trimethylpentyl)-1-hydroxy-4-methyl-2(1H)-pyridone, amorolfine and butenafine in an amount of from 0.25 to 20 percent by weight, preferably 2 to 15 percent by weight, and an antimycotic from the group of itraconazole, terbinafine and fluconazole in an amount of from 0.05 to 10 percent by weight, preferably 0.1 to 5 percent by weight.

6. A process for producing the pharmaceutical preparation as claimed in one or more of claims 1 to 5, which comprises mixing the physiologically acceptable lacquer base in dissolved form with the antimycotics, and further processing the preparation where necessary.

7. The use of the preparation as claimed in one or more of claims 1 to 5 for producing a pharmaceutical [lacuna] for the prophylactic and therapeutic treatment of fungal infections of the toenails and fingernails.

8. The use of a water-insoluble film former as set forth in claims 1 to 5, at least one antimycotic from the group of itraconazole, terbinafine and fluconazole and/or physiologically tolerated salts of itraconazole, terbinafine and fluconazole, and at least one antimycotic from the group of ciclopirox, 6-(2,4,4-trimethylpentyl)-1-hydroxy-4-methyl-2(1H)-pyridone, amorolfine and butenafine and/or physiologically tolerated salts of ciclopirox, 6-(2,4,4-trimethylpentyl)-1-hydroxy-4-methyl-2(1H)-pyridone, amorolfine and butenafine, or a mixture of

more than one of the abovementioned antimycotics or salts thereof, for producing a topical pharmaceutical preparation for the prophylactic and therapeutic treatment of fungal infections of the toenails and fingernails.

9. The use of a preparation as claimed in one or more of claims 1 to 5 in cosmetics.